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(54) ILLUDIN ANALOGS USEFUL AS ANTITUMOR AGENTS

ILLUDIN ANALOGE VERWENDET ALS ANTITUMORMITTEL

ANALOGUES D'ILLUDINE UTILES EN TANT QU'AGENTS ANTITUMORAUX

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Description

Background of the Invention

[0001] A listing of human cancers for which chemotherapy has exerted a predominant role in increasing life span, approaching normal life expectancy, includes Burkitt's lymphoma, acute lymphocytic leukemia and Hodgkin's disease, along with about 10-15 other tumor types. For example, see A. Golden et al., Eur. J. Cancer, 17, 129 (1981) (Table 1). While the cure rate of these cancers illustrates the level of success of screening systems in selecting antitumor agents that are effective in man, these responsive tumors represent only a small fraction of the various types of cancer and, notably, there are relatively few drugs highly active against clinical solid tumors. Such drugs include cyclophosphamide, adriamycin, 5-FU, bexamethylmelamine and the like. Thus, patients with many types of malignancies remain at significant risk for relapse and mortality.

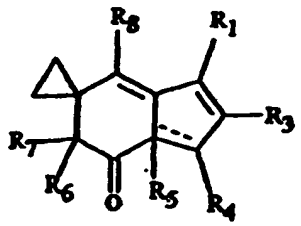
[0002] After relapse, some patients can be reinduced into remission with their initial treatment regimen. However, higher doses of the initial chemotherapeutic agent or the use of additional agents are frequently required, indicating the development of at least partial drug resistance. Recent evidence indicates drug resistance can develop simultaneously to several agents, including ones to which the patient was not exposed. The development of multiple-drug resistant (mdr) tumors may be a function of tumor mass and constitutes a major cause of treatment failure. To overcome this drug resistance, high-dose chemotherapy with or without radiation and allogenic or autologous bone marrow transplantation can be employed. The high-dose chemotherapy may employ the original drug(s) or be altered to include additional agents. The development of new drugs non-cross resistant with mdr phenotypes is required to further the curative potential of current regimens and to facilitate curative interventions in previously treated patients.

[0003] Recently, the in vitro anti-tumor activity of a novel class of natural products called illudins was examined by Kelner, M. et al., Cancer Res., 47, 3186 (1987). Illudin M was purified and submitted for evaluation to the National Cancer Institute Division of Cancer Treatment (NCI DCT) in vivo drug screening program. Illudin M significantly increased the life span of rats with Dunning leukemia, but had a low therapeutic index in solid tumor systems. The extreme toxicity of illudins has prevented any applications in human tumor therapy. Recently, synthetic analogs of the illudins have been developed which exhibit promising antitumor activity, including U.S. Patent Nos. 5,439,936 and 5,523490 and McMorris et al. Experientia 52 (1996) 75-80. Methods of inhibiting tumour cell growth using illudin analogues have also been developed, e.g. as described in WO 91/04754, WO 94/18151 and US Patent No. 5,439,942.

[0004] However, there exists a continuing need for chemotherapeutic agents which inhibit tumor growth, especially solid tumor growth, and which have an adequate therapeutic index to be effective for in vivo treatment.

Summary of the Invention

[0005] The present invention provides illudin analogs of the general formula (I)



(I)

wherein R_1 is $(CH_2)_n$-(X)-(Y); n is 0-4, X is O or S or NH, and Y is $CH_2OC(O)(C_1$-$C_4)$ alkyl, (C_1-C_8alkyl optionally substituted with 2 OH or 1-2 halo (Cl, Br, I or F); a monosaccharide, preferably fructose; $CH_2C(O)$-O-$(CH_2)_2$-O-C(O) CH_2SH, $(CH_2)_2$-O-$(CH_2)_2W$ wherein W is halo; (C_1-C_8)alkyl-O-(C_1-C_8)alkyl; (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_4)alkyl or $C(O)O(C_6$-$C_{10})$aryl, wherein the aryl moiety is optionally substituted with 1-2 OH, halo, (C_1-C_4)alkyl or O(C_1-C_4)alkyl; $CH_2CO_2(C_1$-$C_4)$alkyl, CH_2CO_2H, Si((C_1-C_4)alkyl)$_3$, an amino acid residue, preferably alanyl; or H with the proviso that when Y is H, n is 2-4;

R_3 is H or (C_1-C_4)alkyl;

R_4 is H, $SCH_2CO_2(C_1$-$C_4)$alkyl, O-(C_5-C_{12})aryl or S-(C_5-C_{12})aryl where aryl is optionally substituted with halo,

OH or (C_1-C_4)alkyl;
R_5 is H, OH or absent;
R_6 is (C_1-C_4)alkyl or H; and
R_7 is OH or OSi((C_1-C_4)alkyl)$_3$; or
R_6 and R_7 together are ethylenedioxy;
R_8 is (C_1-C_4)alkyl, optionally substituted with OH or halo;
the bond represented by — is present or absent; and
the pharmaceutically acceptable salts thereof.

[0006] These compounds are useful as antineoplastic agents, i.e., to inhibit tumor cell growth in vitro or in vivo, in mammalian hosts, such as humans or domestic animals, and are particularly effective against solid tumors and multi-drug resistant tumors.

[0007] Thus, the present invention provides a therapeutic method to treat cancer, i.e., to inhibit tumor cell growth in vitro, or preferably, in vivo, by administration to a mammal, such as a human cancer patient, of an amount of a compound of formula I effective to inhibit the growth of said cancer cells, i.e., tumor cells. The present compounds may be particularly useful for the treatment of solid tumors for which relatively few treatments are available. Such tumors include epidermoid and myeloid tumors, acute (AML) or chronic (CML), as well as lung, ovarian, breast and colon carcinoma. The present compounds can also be used against endometrial tumors, bladder cancer, pancreatic cancer, lymphoma, Hodgkin's disease, prostate cancer, sarcomas and testicular cancer as well as. against tumors of the central nervous system, such as brain tumors, neuroblastomas and hematopoietic cell cancers such as B-cell leukemia/lymphomas, myelomas, T-cell leukemia/lymphomas, and small cell leukemia/lymphomas. These leukemia/lymphomas could be either acute (ALL) or chronic (CLL).

[0008] The present compounds may also be targeted to a particular tumor by attaching the compound to a reagent which is capable of binding to a tumor-associated antigen. The antigen may be located on a tumor or in the tumor cell area. Suitable reagents include polyclonal and monoclonal antibodies. The compound-reagent complex may further comprise a linker for attaching the compound to the reagent.

[0009] The present invention also provides pharmaceutical compositions, such as pharmaceutical unit dosage forms, comprising an effective anti-neoplastic amount of one or more of the present illudin analogs in combination with a pharmaceutically acceptable carrier.

[0010] As used herein, with respect to the present method, the term "inhibit" means either decreasing the tumor cell growth rate from the rate which would occur without treatment, or causing the tumor cell mass to decrease in size. Inhibiting also includes causing a compete regression of the tumor. Thus, the present analogs can either be cytostatic of cytotoxic to the tumor cells.

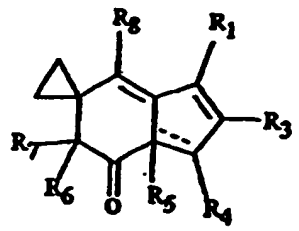
[0011] The subject can be any mammal having a susceptible cancer, i.e., a malignant cell population or tumor. The analogs are effective on human tumors in vivo as well as on human tumor cell lines in vitro.

Brief Description of the Drawings

[0012] Figure 1 is a schematic of representative compounds of the invention

Detailed Description of the Invention

[0013] The present invention provides illudin analogs of the general formula (I)



(I)

wherein R_1 is $(CH_2)_n$-(X)-(Y); n is 0-4, X is O or S or NH; and Y is $CH_2OC(O)(C_1$-$C_4)$ alkyl, (C_1-C_8)alkyl optionally

substituted with 2 OH or 1-2 halo, a monosaccharide, preferably fructose, $CH_2C(O)$-O-$(CH_2)_2$-O-$C(O)CH_2SH$, $(CH_2)_2$-O-$(CH_2)_2W$ where W is halo; $(C_1$-$C_8)$alkyl-O-$(C_1$-$C_8)$alkyl, preferably $(C_1$-$C_4)$alkyl-O$(C_1$-C4)alkyl; $(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_4)$alkyl or C(O)O$(C_6$-$C_{10})$aryl wherein the aryl moiety is optionally substituted with 1-2 OH, halo, $(C_1$-$C_4)$alkyl or O$(C_1$-$C_4)$alkyl; $CH_2CO_2(C_1$-$C_4)$alkyl, CH_2CO_2H, Si$((C_1$-$C_4)$alkyl$)_3$, an amino acid residue, preferably alanyl; or H with the proviso that when Y is H, n is 2-4;

R_3 is H or $(C_1$-$C_4)$alkyl;

R_4 is H, $SCH_2CO_2(C_1$-$C_4)$alkyl, O-$(C_5$-$C_{12})$aryl or S-$(C_5$-$C_{12})$aryl where aryl is optionally substituted with halo, OH or $(C_1$-$C_4)$alkyl;

R_5 is H, OH or absent;

R_6 is $(C_1$-$C_4)$alkyl or H;

R_7 is OH or O(Si$((C_1$-$C_4)$alkyl$)_3$; or

R_6 and R_7 together are ethylenedioxy;

R_8 is $(C_1$-$C_4)$alkyl, optionally substituted with OH or halo; and

the bond represented by --- is present or absent.

[0014] In a particularly preferred embodiment, R_1 is $(CH_2)_n$-X-Y where n is 1, X is O or S and Y is $(C_1$-$C_8)$alkyl optionally substituted with 2 OH or 1-2 halo, or -$C(CH_3)_2O(C_1$-$C_4)$alkyl; where preferably R_5 is absent; R_3, R_6 and R_8 are CH_3; R_4 is H; and R_7 is OH.

[0015] As used herein, the term "alkyl" includes branched or straight-chain alkyl groups.

[0016] As used herein, the term "monosaccharides" includes compounds comprising up to 8 carbons, preferably up to 6 carbons. The term includes glucose, fructose and ribose, as well as deoxy sugars such as deoxyribose and the like.

[0017] The compounds shown in Figure 1 are representative of the present invention.

[0018] The compounds of the present invention may be derived from illudin S, 6-hydroxymethyl acylfulvene (HMAF, i.e., the compound of formula (I) wherein R_1 is CH_2OH, R_3 is CH_3, R_4 is H, R_5 is absent, R_6 is CH_3, R_7 is OH and R_8 is CH_3) and fulvene (i.e., a compound of formula (I) wherein R_1 is H, R_2, R_3 is CH_3, R_4 is H, R_5 is absent, R_6 is CH_3, R_7 is OH and R_8 is CH_3) the syntheses of which are known in the art (see e.g., WO 91/04754; WO 94/18151).

[0019] The following compounds of formula (I) where X is S or O, may be prepared by adding the appropriate reagent to an acidic solution of HMAF, unless otherwise noted.

[0020] Where Y is $(C_1$-$C_8)$alkyl, an alkyl ether is used. For example, compound **16** (where Y is ethyl) was prepared using ethyl ether. Where Y is $(C_1$-$C_8)$alkyl substituted with 2 OH or 1-2 halogen, the appropriate alcohol or thiol, halogenated where required, was added. For example, for compounds **19** and **20** where X is O and Y is 2,3 dihydroxypropyl and 2-bromo ethyl; glycerol and 2-bromoethanol respectively, were used. Compounds wherein Y is $CH_2OC(O)(C_1$-$C_4)$ alkyl, are prepared by reacting compounds wherein R_1 is $(CH_2)_nOCH_2OH$ with $(C_1$-$C_4)$alkyl C(O)Cl in the presence of base. Compound **53** was formed as a by product in the synthesis of compound **20.** For compound **32,** where X is S and Y is 2,3 dihydroxypropyl, thioglycerol was employed as the reagent.

[0021] The appropriate saccharide is used to synthesise compounds of formula (I) where Y is a monosaccharide. For example, compound **18** was made using fructose.

[0022] Where Y is $CH_2C(O)$-O$(CH_2)_2$-O-$C(O)CH_2SH$, i.e., compound **51**, a controlled amount of glycol dimercaptoacetate is employed as the reagent.

[0023] Where Y is $(CH_2)_2$-(O)-$(CH_2)_2W$ where W is halo, the appropriate halogenated alcohol is used. For example, compound **53** was obtained by adding 2-bromoethanol.

[0024] Compounds of formula (I) where Y is $(C_1$-$C_8)$alkyl-O-$(C_1$-$C_8)$alkyl where $(C_1$-$C_8)$alkyl is straight chain alkyl, may be prepared using a method analogous to that used to prepare compound **53**. Where $(C_1$-$C_8)$alkyl is branched, the desired product may be obtained by the addition of an appropriate alkene to HMAF along with a catalytic amount of $POCl_3$. For example, compound **21**, where Y is 2-methoxy-2-prop-yl, was prepared by adding 2-methoxypropene to HMAF.

[0025] Where Y is $(C_6$-$C_{10})$alkyl or $(C_6$-$C_{10})$alkyl$(C_1$-$C_4)$alkyl, compounds may be prepared using a thioaryl or aryl mercaptan as the reagent. For example, compound **23**, where Y is $(C_6H_4)OH$, was prepared by adding 4-hydroxythiophenol. Compound **24** was prepared by adding benzyl mercaptan to an acidic solution of HMAF. Compound **26**, where X is S and Y is 4-methylbenzene, was prepared by adding *p*-thiocresol to an acidic solution of HMAF. Compound **48**, where Y is 4-methylbenzene and R_4 is thiocresol, was obtained as a by product when limited *p*-thiocresol was used to prepare compound **26**. Compounds **49** and **50**, where n=0, X is S, Y is 4-methylbenzene and R_4 is H or thiocresol, respectively, were prepared by adding *p*-thiocresol to an acidic solution of acylfulvene. Compounds where Y is C(O)O$(C_6$-$C_{10})$aryl may be prepared by adding the appropriate aryl chloroformate to a basic solution of HMAF. For example, compound **27**, where Y is phenylacetate, was prepared by adding phenyl chloroformate and pyridine to a solution of HMAF.

[0026] Compounds where Y is $CH_2CO_2(C_1$-$C_4)$alkyl and X is S may be prepared by adding the appropriate thiol to an acidic solution of HMAF. For example, compound **25** where Y is CH_2CO_2Me and R_4 and R_5 are H, was prepared by adding methylthioglycolate to an acidic solution of HMAF in acetone. Compounds **30** and **31** where Y is CH_2CO_2Me,

R_4 is CH_2CO_2Me and R_5 is H and OH, respectively, were prepared by adding methylthioglycolate to a neutral solution of HMAF in acetone and THF.

[0027] Compounds where Y is CH_2CO_2H may be prepared via hydrolysis of the corresponding esters. For example, compound **29** was prepared as a by product in the synthesis of compound **25** described above. Alkali metal, alkaline earth metal and amine salts of the CO_2H group are also within the scope of the invention.

[0028] Where Y is $Si((C_1\text{-}C_4)alkyl)_3$, the appropriate silanating reagent is added to a solution of HMAF and imidazole. For example, compounds **43** and **44** where R_1 is triethylsiloxy and R_7 is OH or triethylsiloxy, respectively, were both obtained when triethylsilylchloride was added to a solution of HMAF and imidazole in DMF.

[0029] Where Y is an amino acid residue, for example. glycyl or alanyl, the appropriate thiol containing amino acid analog may be used, such as cysteine and analogs thereof. For example, compound **37**, where Y is glycyl, was prepared by adding cysteine to an acidic solution of HMAF.

Compounds where X is O, Y is H and n is 2-4 may be obtained via reduction of the corresponding aldehyde or acid with an appropriate reducing agent. For example, compound **9** was obtained via reduction of the corresponding aldehyde compound with sodium cyanoborohydride and acetic acid.

[0030] Pharmaceutically acceptable salts include, where applicable, salts such as amine acid addition salts and the mono-, di- and triphosphates of free hydroxyl groups. Amine salts include salts of inorganic and organic acids, including hydrochlorides, sulfates, phosphates, citrates, tartarates, malates, maleates, bicarbonates, and the like. Alkali metal amine or ammonium salts can be formed by reacting hydroxyaryl groups with metal hydroxides, amines or ammonium.

[0031] The compounds of the present invention can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human cancer patient, in a variety of form adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intraperitoneal, intramuscular or subcutaneous routes.

[0032] Thus, the present compounds may be orally administered, for example, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules. may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules. elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

[0033] The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

[0034] The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0035] The pharmaceutical dosage forms suitable for infection or infusion use can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable of infusible solutions or dispersions. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersion or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, or example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin. Sterile injectable solutions are prepared

by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

[0036] Useful dosages of the compounds of Figure (I) can be determined by correlating their in vitro activity, and in vivo activity in animal models, such as murine or dog models as taught for illudin analogs such as those of U.S. Patent Nos. 5,439,936 and 5,523,490, to activity in higher mammals. such as children and adult humans as taught, e.g., in Borch et al. (U.S. Patent No. 4,938,949).

[0037] The therapeutically effective amount of analog necessarily varies with the subject and the tumor to be treated. However, it has been found that relatively high doses of the analogs can be administered due to the decreased toxicity compared to illudin S and M. A therapeutic amount between 30 to 112,000 µg per kg of body weight is especially effective for intravenous administration while 300 to 112,000 pg per leg of body weight is effective if administered intraperitoneally. As one skilled in the art would recognize, the amount can be varied depending on the method of administration.

[0038] The invention will be further described by reference to the following detailed examples.

EXAMPLES

EXAMPLE I - Synthesis of illudin analogs

[0039] **General.** Melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured at 300 and 75 MHz. High resolution mass spectra were determined at the University of Minnesota Mass Spectrometry Service Laboratory. All chromatography used silica gel (Davisil 230-425 mesh, Fisher Scientific) and solvent was ethyl acetate and hexanes except being mentioned specifically. Analytical TLC was carried out on Whatman 4420 222 silica gel plates. Reactions were routinely monitored by TLC.

[0040] Synthesis of illudin S, hydroxymethylacylfulvene (HMAF and fulvene are known in the art (see, e.g., WO 91/04754; WO 94/18151).

[0041] **Compound 23.** To the solution of 170 mg HMAF (MW 246, 0.691 mmol) in 15 ml acetone and 1 M H_2SO_4 solution (1:1) was added 63 mg 4-hydroxyl thiophenol (MW 126, 0.5 mmol). The mixture was stirred at room temperature for two hours and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 128 mg **23** (72.3%) as yellow gum: IR (KBr) 3360, 2974, 1646, 1592, 1588, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (m, 1H), 1.09 (m, 1H), 1.38 (m, 1H), 1.42 (s, 3H), 1.52 (m, 1H), 1.70 (s, 3H), 2.14 (s, 1H), 3.96 (q, J_{AB} = 13.2 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 7.07 (s, 1H), 7.20 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 197.9, 159.6, 156.7, 142.4, 138.2, 136.0, 135.9, 132.9, 131.5, 125.8, 123.6, 116.1, 115.9, 76.2, 37.6, 34.2, 27.8, 16.3, 14.2, 12.5, 9.5; MS m/z 354 (M^+), 298,270,229; HRMS for $C_{21}H_{22}O_3S$ calcd 354.1296, found 354.1286; UV λmax (methanol) 332 nm (ε 7844).

[0042] **Compound 24.** To the solution of 117 mg HMAF (MW 246, 0.475 mmol) in 15 ml acetone and 1 M H_2SO_4 solution (1:1) was added 46 mg benzyl mercaptan (MW 124, 0.371 mmol). The mixture was stirred at room temperature for overnight and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 100 mg **24** (76.6%) as yellow gum: IR (KBr) 3451, 2980, 1659, 1598, 1496, 1097 cm^{-1}, ^{1}HNMR ($CDCl_3$) δ 0.64(m, 1H), 1.02(m, 1H), 1.29 (m, 1H), 133 (s, 3H), 1.46 (m, 1H), 1.91 (s, 3H), 1.98 (s, 3H), 3.62 (s, 2H), 3.71 (s, 2H), 7.06 (s, 1H), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 197.2, 159.5, 141.8, 138.4, 137.8, 134.9, 130.1, 128.7, 128.3, 126.9, 126.0, 75.9, 37.5, 36.8, 28.6, 27.5, 15.7, 14.1, 12.9, 9.3; MS m/z 3,52 (M^+), 294, 229; HRMS for $C_{22}H_{24}O_2S$ calcd 352.1497, found 352.1488; UV λmax (methanol) 332 nm (ε 8431).

[0043] **Compound 25 & 29.** To the solution of 166 mg HMAF (MW 246, 0.675 mmol) in 15 ml acetone and 1 M H_2SO_4 solution (1:1) was added 51 mg methyl thioglycolate (MW 106, 0.481 mmol). The mixture was stirred at room temperature for overnight and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 59mg **25** (36.7%) and 94 mg **29** (61.1%). **25** is a yellow gum: IR (KBr) 3451, 2944, 1731, 1665, 1592, 1496, 1278 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (m, 1H), 1.07 (m, 1H), 1.35 (m, 1H), 1.37 (s, 3H), 1.49 (m, 1H), 2.12 (s, 3H), 2.16 (s, 3H), 3.23 (s, 2H), 3.74 (s, 3H), 3.92 (q, J_{AB} = 12.3 Hz, 2H), 7.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 197.5, 170.7, 159.6, 142.5, 138.3, 134.7, 129.1, 126.5, 76.1, 52.3, 37.6, 33.2, 29.6, 27.5, 16.1, 14.2, 12.9, 9.5; UV λmax (methanol) 334 nm (ε 8093). **29** is also a yellow gum: ^1H NMR ($CDCl_3$) δ 0.73 (m, 1H), 1.09 (m, 1H), 1.32 (m, 1H), 1.37 (s, 3H), 1.50 (m, 1H), 2.12 (s, 3H), 2.16 (s, 3H), 3.25 (s, 2H), 3.93 (m, 2H), 7.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 197.8, 174.7, 159.8, 142.7, 138.2, 135.1, 129.4, 126.4, 76.1, 37.7, 33.2, 29.6, 27.6, 16.2, 14.3, 12.9, 9.5

[0044] **Compound 26.** To the solution of 125 mg HMAF (MW 246, 0.508 mmol) in 20 ml acetone and 1 M H_2SO_4 solution (1:1) was added 59 mg p-thiocresol (MW 124, 0.476 mmol). The mixture was stirred at room temperature for 5 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 127 mg **26** (75.8%) as yellow gum: IR (KBr) 3456, 2972, 1663, 1596, 1500, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (m, 1H), 1.07 (m, 1H), 1.32 (m, 1H), 1.38 (s, 3H), 1.50 (m, 1H), 1.82 (s, 3H), 2.14 (s, 3H), 2.31 (s, 3H), 3.97 (s, 1H), 4.04 (q, JAB = 12.9 Hz, 2H), 7.05 (s, 1H), 7.07 (d, q = 8.1 Hz, 2H), 7.23 (d, q= 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 197.3, 159.2, 142.3, 138.4, 137.3, 135.0, 132.2, 131.3, 129.8, 129.5, 126.1, 76.0, 37.5, 33.1, 27.6, 21.0, 16.1, 14.1, 12.6, 9.4; MS m/z 352 (M^+), 297, 250, 229; HRMS for $C_{22}H_{24}O_2S$ calcd 352.1497, found 352.1499; UV λmax (methanol) 333 nm (ε 6598).

[0045] **Compound 32.** To the solution of 195 mg HMAF (MW 246, 0.793 mmol) in 10 ml acetone and 1 M H_2SO_4 solution (1:1) was added 70.2 mg thioglycerol (MW 92, 0.763 mmol). The mixture was stirred at room temperature for 20 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 147 mg **32** (78.3%) as yellow gum: IR (KBr) 3385, 2908, 1658, 1586, 1495, 1284 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (m, 1H), 1.09 (m, 1H), 1.26 (m, 1H), 1.36 (s, 3H), 1.49 (m, 1H), 2.10 (s, 3H), 2.16 (s, 3H), 2.65 (m, 3H), 3.81 (m, 5H), 4.03 (s, 1H), 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 197.6, 159.6, 141.8, 138.2, 135.1, 130.4, 126.2, 76.1, 70.7, 70.6, 65.2, 37.6, 35.2, 35.1, 29.5, 29.4, 27.6, 16.3, 14.2, 13.1, 9.5; MS m/z 336 (M^+), 261, 229, 201; HRMS for $C_{18}H_{24}O_4S$ calcd 336.1395, found 336.1395; UV λmax (methanol) 332 nm (ε 6893).

[0046] **Compound 16.** To the solution of 22 mg HMAF (MW 246, 0.089 mmol) in 3 ml acetone and 1 M H_2SO_4 solution (1:1) was added 7.5 ml ethyl ether. The mixture was stirred at room temperature for 24 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 17 mg **16** (80.2%) as yellow gum: IR (KBr) 3457, 2968, 1659, 1592, 1502, 1284, 1097 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (m, 1H), 1.08 (m, 1H), 1.23 (t, J=6.9 Hz, 3H), 1.33 (m, 1H), 1.38 (s, 3H), 1.48 (m, 1H), 2.11 (s, 3H), 2.14 (s, 3H), 3.53 (q, J = 6.9 Hz, 2H), 3.91 (s, 1H), 4.42 (q, J_{AB} = 10.7, 2H), 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 197.4, 159.5, 142.2, 138.8, 134.3, 130.0, 126.4, 75.8, 65.0, 63.5, 37.2, 27.2, 15.6, 14.8, 13.8, 12.7, 9.0; MS m/z 274 (M^+), 261, 228, 200, 185; HRMS for $C_{17}H_{22}O_3$ calcd 274.1569, found 274.1568; UV λmax (methanol) 330 nm (ε 7225).

[0047] **Compound 18.** To the solution of 1.5 g HMAF (MW 246, 6.098 mmol) in 66 ml acetone and 40 ml 1 M H_2SO_4 solution (1:1) was added 20 g fructose. The mixture was stirred at room temperature for overnight and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed (use methylene chloride and methanol as solvents) to give 350 mg **18** (14.1%, mixture) as yellow gum (with 701 mg HMAF recycled); IR (KBr) 3397, 2932, 1659, 1574, 1369, 1085 cm^{-1}; MS m/z 409 (M+H), 307, 229, 203; HRMS for $C_{21}H_{28}O_8$ (M+H) calcd 409.1863, found 409.1869; UV λmax (methanol) 332 nm (ε 4745).

[0048] **Compound 19.** To the solution of 110 mg HMAF (MW 246, 0.447 mmol) in 15 ml acetone and 1 M H_2SO_4 solution (1:1) was added 5 ml glycerol. The mixture was stirred at room temperature for 22 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed (add 5% methanol to the normal solvent system) to give 79 mg **19** (55.2%) as yellow gum (with 40 mg HMAF recycled): IR (KBr) 3415, 2926, 1659, 1586, 1103 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (m, 1H), 1.08 (m, 1H), 1.26 (m, 1H), 1.37 (s, 3H), 1.50 (m, 1H), 2.10 (s, 3H), 2.15 (s, 3H), 2.57 (s, 1H), 3.58 (m, 4H), 3.86 (m, 1H), 3.91 (s, 1H), 4.51 (q, J_{AB}= 12.9 Hz, 2H), 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 198.0, 160.1, 143.2, 138.8, 134.6, 129.4, 126.9, 76.2, 70.9, 70.6, 64.4, 63.8, 37.6, 27.4, 16.1, 14.2, 13.1, 9.4; MS m/z 320 (M^+), 277, 228, 185; HRMS for $C_{18}H_{24}O_5$ calcd 320.1623, found 320.1616; UV λmax (methanol) 331 nm (ε 7920).

[0049] **Compound 20 & 53.** To the solution of 188 mg HMAF (MW 246, 0.764 mmol) in 10 ml acetone and 1 M H_2SO_4 solution (1:1) was added 5 ml 2-bromoethanol. The mixture was stirred at room temperature for 4.5 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 179.2 mg **20** (66.4%) as yellow gum: IR (KBr) 3445, 2914, 1650, 1592, 1502, 1097 cm^{-1}; ^1H NMR ($CDCl_3$,) δ 0.71 (m, 1H), 1.07 (m, 1H), 1.35 (m, 1H), 1.38 (s, 3H), 1.48 (m, 1H), 2.15 (s, 3H), 3.47 (t, J = 6.0 Hz, 2H), 3.77 (t, J= 6.0 Hz, 2H), 3.91 (s, 1H), 4.54 (q, J_{AB} = 12 Hz, 2H), 7.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 198.1, 160.6, 143.2, 138.9, 134.4, 129.3, 127.0, 76.3, 69.4, 64.1, 37.7, 30.6, 27.6, 16.4, 14.3, 13.2, 9.5; MS m/z 352 (M - H), 326, 228, 285; HRMS for $C_{17}H_{21}BrO_3$ (M - H) calcd 352.0674, found 352.0671; UV λmax (methanol) 332 nm (ε 7777). **53** was obtained as by product as a yellow gum: ^1H NMR ($CDCl_3$) δ 0.72 (m, 1H), 1.05 (m, 1H), 1.32 (m, 1H), 1.37 (s, 3H), 1.50 (m, 1H), 2.13 (s, 3H), 2.15 (s, 3H), 3.46 (t, J = 6.3 Hz, 2H), 3.65 (m, 4H), 3.79 (t, J = 6.3 Hz, 2H), 3.90 (s, 1H), 4.51 (q, J_{AB} = 12 Hz, 2H), 7.09 (s, 1H).

[0050] **Compound 21.** To the solution of 260 mg HMAF (MW 246, 1.057 mmol) in 6 ml 2-methoxyl propene was added 2 drops $POCl_3$. The mixture was stirred at room temperature for 6 days and was partitioned between ethyl

acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 133 mg **21** (39.6%) as yellow gum (with 87 mg HMAF recycled): IR (KBr) 3457, 2980, 1665, 1598, 1502, 1091 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.72 (m, 1H), 1.06 (m, 1H), 1.25 (m, 1H), 1.38 (s,3H), 1.41, (s, 3H), 1.42 (s, 3H), 1.49 (m, 1H), 2.15 (s, 3H), 3.25 (s, 6H), 3.95 (s, 1H), 4.43 (s, 2H), 7.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 197.7, 159.5, 142.2, 134.9, 134.8, 130.5, 126.7, 100.3, 76.1, 54.4, 48.6, 37.4, 27.5, 24.4, 24.3, 15.9, 14.0, 13.0, 9.3; MS m/z 318 (M^+), 260, 229, 185, 73; HRMS for $C_{19}H_{26}O_4$ calcd 318.1831, found 318.1823; UV λmax (methanol) 330 nm (ε8728).

[0051] Compound 30 & 31. To the solution of 108 mg HMAF (MW 246, 0.439 mmol) in 40 ml acetone and THF (1:1) was added 1.5 ml methyl thioglycolate. The mixture was stirred at room temperature for 4 days and was partitioned between ethyl acetate and water. The organic extracts were dried by $MgSO_4$, concentrated and chromatographed to give 44 mg **30** and 20 mg **31**. **30** is a yellow gum: ^1h NMR ($CDCl_3$) δ 0.70 (m, 1H), 1.09 (m, 1H), 1.33 (s, 3H), 1.35 (m, 1H), 1.50 (m, 1H), 2.14 (s, 3H), 2.15 (s, 3H), 3.23 (s, 2H), 3.67 (s, 3H), 3.74 (s, 3H), 3.92 (s, 2H), 4.08 (m, 3H); MS m/z 438 (M^+), 424, 333, 315; HRMS for $C_{21}H_{26}O_6S_2$ calcd 438.1172, found 438.1188; UV λmax (methanol) 372 nm (ε 10760), 243 run (ε 14364). **31** is a light yellow gum: ^1H NMR ($CDCl_3$) δ 0.46 (m, 1H), 0.88 (m, 1H), 1.04 (m, 1H), 1.32 (s, 3H), 1.38 (m, 1H), 1.87 (s, 3H), 2.03 (s, 3H), 3.13 (m, 2H), 3.44 (m, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 4.02 (s, 1H), 4.41 (q, 2H); MS m/z 456 (M^+), 425, 351, 333; HRMS for $C_{21}H_{28}O_7S_2$ calcd 456.1277, found 456.1288; UV λmax (methanol) 263 nm (∈ 17264), 204 nm (e 8648).

[0052] Compound 9. To the solution of 1 g fulvene (MW 216, 4.63 mmol) in 5 ml acetone and 2.5 ml 2 M H_2SO_4 solution was added 2.5 ml acrolein. The mixture was stirred at room temperature for 7 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 378 mg compound x (30.0%). Compound *x* is a yellow gum: 0.68 (m, 1H), 1.07 (m, 1H), 1.32 (m, 1H), 1.36 (s, 3H), 1.46 (m, 1H), 2.01 (s, 3H), 2.06 (s, 3H), 2.65 (t, J = 7.8 Hz, 2H), 3.00 (m, 2H), 3.93 (s, 1H), 7.12 (s, 1H), 9.83 (s, 1H); ^{13}C NMR (CDC^3) δ 200.4, 196.3, 157.3, 139.4, 138.3, 135.4, 133.7, 125.3, 75.4, 43.5, 36.9, 27.0, 19.5, 15.4, 13.4, 12.4, 8.6; MS m/z 272 (M^+), 244, 215, 201; HRMS for $C_{17}H_{20}O_3$ calcd 272.1413, found 272.1416; UV λmax (methanol) 332 nm (ε 8500). To the solution of 30 mg compound x (MW 272, 0.110 mmol) in 5 ml THF was added 5 drops HOAc and some sodium cyanoborohydride. The mixture was stirred at room temperature for 1 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated NH_4Cl and saline respectively to netural. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 21 mg **9** (69.5%) as yellow gum: ^1H NMR ($CDCl_3$) δ 0.67 (m, 1H), 1.06 (m, 1H), 1.26 (m, 1H), 1.36 (s, 3H), 1.46 (m, 1H), 1.73 (m, 2H), 2.06 (s, 3H), 2.07 (s, 3H), 2.74 (m, 2H), 3.70 (t, J = 6.3 Hz, 2H), 3.96 (s, 1H), 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 197.0, 157.7, 139.6, 139.0, 136.6, 136.5, 128.2, 75.9, 62.0, 37.3, 33.0, 27.5, 24.0, 15.9, 13.8, 12.8, 9.0; MS m/z 274 (M^+), 246, 215, 187; HRMS for $C_{17}H_{22}O_3$ calcd 274.1569, found 274.1557; UV λmax (methanol) 330 nm (ε 6700).

[0053] Compound 27. To the solution of 163 mg HMAF (MW 246, 0.663 mmol) in 10 ml methylene chloride was added 0.18 ml pyridine and 0.34 ml phenyl chloroformate at 0°C under argon. The mixture was stirred for 3 h and was partitoned between ethyl acetate and water. The organic extracts were washed with saline. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 20 mg **27** as yellow gum: ^1H NMR ($CDCl_3$) δ 0.85 (m, 1H), 1.18 (m, 1H), 1.43 (m, 1H), 1.52 (s, 3H), 1.61 (m, 1H), 2.12 (s, 3H), 2.28 (s, 3H), 4.04 (s, 1H), 5.06 (q, J_{AB} = 11.1 Hz, 2H), 6.93-7.47 (m, 6H).

[0054] Compound 28. To the solution of 116 mg HMAF (Mw 246, 0.447 mmol) in 10 ml methylene chloride was added 0.10 ml pyridine and 0.25 ml benzyl chloride under argon. The mixture was concentrated and chromatographed to give 152 mg **28** (92.1%) as yellow gum (with 13 mg HMAF recycled): ^1H NMR ($CDCl_3$) δ 0.65 (m, 1H), 1.02 (m, 1H), 1.18 (m, 1H), 1.32 (s, 3H), 1.44 (m, 1H), 2.03 (s, 3H), 2.16 (s, 3H), 3.86 (s, 1H), 5.28 (q, J_{AB} = 13.2 Hz, 2H), 7.06 (s, 1H).

[0055] Compound 43 & 44. To the solution of 340 mg HMAF (MW 246, 1.38 mmol) and 110 mg imidazole (MW 68, 1.62 mmol) in 4 ml DMF was added 0.7 ml triethylsilyl chloride (d 0.898, MW 360, 1.75 mmol). The mixture was stirred at room temperature for one and half an hour. The mixture was partitioned between ethyl eter and saturated $NaHCO_3$. The ether extract was then washed by saline and dried by $MgSO_4$. After filtration and concentration, it was chromatographed to give 30 mg **43** and 41.7 mg **44**. **43** is a yellow gum: ^1H NMR ($CDCl_3$) δ 0.62 (m, 10H), 0,94 (t, J = 7.5 Hz, 6H), 1.06 (m, 1H), 1.34 (m, 1H), 1.38 (s, 3H), 1.47 (m, 1H), 2.12 (s, 3H), 2.18 (s, 3H), 3.92 (s, 1H), 4.63 (q, J_{AB} = 12.6 Hz, 2H), 7.09 (s, 1H). **44** is also a yellow gum: ^1H NMR ($CDCl_3$) δ 0.65 (m, 19H, 0.87 (t, J = 7.8 Hz, 12H), 1.00 (m, 1H), 1.17 (m, 1H), 1.30 (d, 3H), 1.36 (m, 1H). 2.03 (d, 3H). 2.09 (s, 3H), 4.55 (q, 2H), 6.96 (s, 1H).

[0056] Compound 48. 48 was formed as a by product when limited thio compound was used to make 26. 48 is a yellow gum: 1H NMR ($CDCl_3$) δ 0.64 (m, 1H), 1.05 (m, 1H), 1.26 (m, 1H), 1.37 (s, 3H), 1.48 (m 1H), 1,84 (s, 3H), 2.16 (s, 3H), 2.28 (s, 3H), 2.32 (s, 3H), 4.04 (s, 2H), 6.87-7.27 (m, 8H); HRMS for $C_{28}H_{28}O_2S_2$ calcd 460.1532, found 160.1504.

[0057] Compound 49 & 50. To a solution of acylfulvene in acetone and 1 M H_2SO_4 solution (1:1) was added p-thiocresol at room temperature. The mixture was stirred for ovenight and partitioned between EtOAc and water The organic extracts were washed by saturated $NaHCO_3$ and saline respectively. After being dried by $MgSO_4$, it was con-

centrated and chromatographed to give **49** and **50** in low yield. **49** is a yellow gum: ^{1}H NMR ($CDCl_3$) δ 0.69 (m,1H), 4.88 (m,1H), 1.06 (m, 1H), 1.25 (m, 1H), 1.37 (s, 3H), 2.16 (s, 3H), 2.22 (s, 3H), 2.28 (s, 3H), 3.90 (s, 1H), 6.90-7.30 (m,5H). **50** is also a yellow gum: ^{1}H NMR ($CDCl_3$) δ 0.63 (m, 1H), 1.06 (m, 1H), 1.25 (m, 1H), 1.37 (s, 3H), 1.45 (m, 1H), 1.83 (s, 3H), 2.16 (s, 3H), 2.28 (s, 3H), 2.32 (s, 3H), 4.04 (s, 1H), 6.87-7.30 (m, 8H).

[0058] **Compound 51.** To a solution of HMAF in acetone and 1M H_2SO_4 (1:1) was added limited glycol dimercaptoacetate at room temperature. The mixture was stared for several hours and worked up as usuat to give **51** as a yellow gum: ^{1}H NMR ($CDCl_3$) δ 0.72 (m, 1H),1.09 (m, 1H), 1.35 (m, 1H), 1.36 (s, 3H), 1.50 (m, 1H), 2.12 (s. 3H), 2.15 (s, 3H), 3.28 (t, 3 - 7.8 Hz, 4H), 3.87 (s, 1H), 3.92 (q, J_{AB}= 13.2,2H),4.36 (s, 4H), 7.08 (s, 1H).

[0059] **Compound 37.** To a solution of HMAF in acetone and 1M H_2SO_4 solution (1: 1) was **1** added equivalent cysteine. The mixture was stirred at room temperature for overnight. Large amount of EtOAc was introduced and the aqueous layer was removed by adding $MgSO_4$. Solid $NaHCO_3$ was also added in order to neutralize the sulfuric acid. The solution was then filtered, concentrated and chromatographed to give **37** as a yellow gum: ^{1}H NMR (CD_3OD) δ 0.78 (m, 1H), 0.89 (m, 1H), 1.06 (m, 1H), 1.31 (s, 3H), 1.43 (m, 1H), 2.15 (s, 3H), 2.21 (s, 3H), 2.91-4.02 (m, 8H), 7.04 (s, 1H).

[0060] **Compounds 56 & 58.** To a solution of HMAF in acetone and 1M H_2SO_4 (1:1) was added equivalent p-hydroxy thiophenol. The mixture was stirred at room temperature for overnight. The mixture was extracted by EtOAc. Then the organic extracts were washed by saturated $NaHCO_3$ and saline respectively. After being dried over $MgSO_4$, the solution was concentrated and chromatographed to give **56 & 58. 56** is a yellow gum: ^{1}H NMR ($CDCl_3$) 0.70 (m, 1H), 0.89 (m, 1H), 1.05 (m, 1H), 136 (s, 3H), 1.51 (m, 1H), 2.16 (s, 3H), 2.21 (s, 3H), 3.92 (s, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.25 (s, 1H); **58** is also a yellow gum: δ 0.62 (m, 1H), 1.04 (m, 1H), 1.24 (m, 1H), 1.34 (s, 3H), 1.47 (m, 1H), 1.79 (s, 3H), 2.15 (s, 3H), 4.07 (s, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H).

EXAMPLE II - *In Vitro* Studies

[0061] To assess cytotoxic ejects, various concentrations of illudins were added to cultures of MV522 (human lung carcinoma cell line) and 8392 (B-cell leukemia/lymphoma) cells for 48 hours, then cell growth/viability was determined by trypan blue exclusion. As an alternative to 48 hour continuous exposure studies, cells were plated in liquid culture in 96 well plates, exposed to various concentrations of illudins for 2 hours, pulsed with [^{3}H]-thymidine for one to two hours and harvested onto glass filters. The filter papers were added to vials containing scintillation fluid and residual radioactivity determined in a beta (scintillation) counter.

	2 hour IC_{50} (nm/l)		48 hour IC_{50} (nm/l)	
Compound	MV522	8392	MV522	8392
8	870±90	12200 ±740	630±80	15100±2200
9	500±33	47100±10950	850±180	15100±2200
21	2400±940	34300±9400	930±250	NT
23	2920±1140	138200±13000	2750±510	NT
24	1780±200	12780±2140	1210±260	NT
25	1300±310	> 25 µm/l	1180±120	NT
32	595±185	> 50 µm/l	205±30	NT

[0062] As shown above, the illudin analogs 8-32 are potent anti-tumor agents.

EXAMPLE III - *In Vivo* Studies

[0063] Several analogs were chosen for in vivo studies. The anticancer agent mitomycin C was used as a pharmaceutical control. Drug therapy was started 10 days after inoculation on a daily basis via IP route for 5 consecutive days. The animals were monitored for 3 weeks after start of therapy. With regard to all analogs administered, the maximum tolerated dose (MTD) was not achieved.

[0064] BALB/c nu/nu 4-week old female mice weighing 18-22 g were obtained from Simonsen, Inc. (Gilroy, CA) and maintained in the athymic mouse colony of the University of California (San Diego, CA) under pathogen free conditions using HEPA filter hoods. Animals were provided with sterilized food and water *ad libitum* in groups of 5 in plastic cages vented with polyester fiber filter covers. Clean, sterilized gowns, glove, face masks, and shoe and hood covers were

worn by all personnel handling the animals. All studies were conducted in accordance with guidelines of the NIH "Guide for Care and Use of Animals" and approved by the University Institutional Animal Care and Use Committee (Protocol 3-006-2)

[0065] The MV522 lung carcinoma line used for xenograft studies was derived as described by Kelner et al. (*Anticancer Res.*, 15: 867-872; 873-878 (1995)) and maintained in antibiotic free RPMI 1640 (Mediatech, Herndon, VA) supplemented with 10% fetal bovine serum and 2 mM glutamine in 37°C humidified carbon dioxide incubator.

[0066] Mice were randomized into treatment groups of five animals each for initial studies and groups of 16-20 animals for confirming analogue efficacy. Each animal was earmarked and followed individually throughout the experiments. Mice received s.c. injections of the parental cell line MV522 using 10 million cells/inoculation over the shoulder. Ten days after s.c. implantation of the MV522 cells, when s.c. tumors were approximately 3 x 3 mm in size, animals received the desired drug and dosage. The effect of the drug on life span was calculated from median survival.

[0067] Although MV522 cells kill mice by metastases, primary s.c. tumor growth over the shoulder was monitored starting on the first day of treatment and at weekly intervals thereafter. Tumor size was measured in two perpendicular diameters. Tumor weights were estimated according to the formula $w = (\text{width})^2 \times \text{length}/2$). Relative weights (*RW*) were calculated to standardized variability in tumor size among test groups at initiation of treatment using the formula $RW = Wt/wi$, where *Wi* is the tumor weight for a given animal at beginning of drug treatment and *Wt* is tumor weight at a subsequent time. Animals were necropsied, and organs were examined for evidence of metastases.

[0068] Comparison of survival curves between groups of animals was by the method of Kaplan and Meir. For comparison of relative tumor weights between multiple groups of animals, ordinary ANOVA followed by Tukey-Kramer multiple Comparison post ANOVA analysis was performed (Kelner et al. (*Anticancer Res.*, 15: 167-872; 873-878 (1995)). Probability values (p) less than 0.05 were considered statistically significant.

Compound	dose (mg/kg)	p value (tumor weight)
HMAF	6	<0.01
	8	<0.01
	10	<0.001
9	4	<0.001
	8	<0.001
	16	<0.001
16	4	<0.001
	8	<0.01
	16	<0.01
18	18	<0.001
	20	<0.001
	24	<0.001
	32	<0.001
19	4	<0.05
	8	<0.001 (toxic)
	16	<0.001 (toxic)
21	4	< 0.01
	8	<0.001
	16	<0.001
22	4	<0.001
	8	<0.001
	16	toxic
23	4	<0.001

(continued)

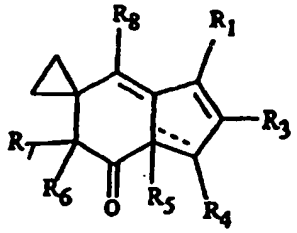
Compound	dose (mg/kg)	p value (tumor weight)
	8	<0.001
	16	<0.001
24	0.2	<0.001
25	4	<0.001
	8	<0.001
	16	<0.001
26	0.4	<0.001
29	4	<0.001
	8	<0.001
	16	<0.001
32	4	<0.05
	8	>0.05
	16	< 0.001
	20	<0.001
	24	<0.001
mitomycin C	1.6	> 0.05
	2.0	toxic

Analog 21 appears to be more efficacious than HMAF particularly in view of the fact that MTD was not achieved. Analogs 16 and 32 were also effective. The high dose mitomycin C bad an effect on tumor size. The dose, however, was toxic as all animals eventually succumbed before day 31. The low dose mytomycin C had little effect.

[0069] The invention has been described with reference to various specific and preferred embodiments and techniques.

Claims

1. A compound of the formula



wherein R_1 is $(CH_2)_n$-X-Y,

where n is 0 to 4;

X is O or S or NH, and

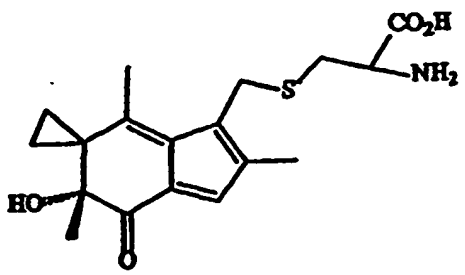
Y is $-CH_2OC(O)$ (C_1-C_4)alkyl, (C_1-C_8)alkyl optionally substituted with 2 OH or 1-2 halo; a monosaccharide, $-CH_2C(O)-O-(CH_2)_2-O-C(O)CH_2SH$, $-(CH_2)_2-O-(CH_2)_2W$ where W is halo; $-(C_1-C_8)$alkyl-O-(C_1-C_8)alkyl; (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_4)alkyl, $C(O)O(C_6-C_{10})$aryl wherein the aryl group is optionally substituted with 1-2 OH, halo, (C_1-C_4)alkyl, or $O(C_1-C_4)$alkyl; $-CH_2CO_2(C_1-C_4)$alkyl, $-CH_2CO_2H$, $Si((C_1-C_4)alkyl)_3$ or an amino acid residue or H;

R_3 is H or $(C_1\text{-}C_4)$alkyl;
R_4 is $SCH_2CO_2(C_1\text{-}C_4)$alkyl, O-$(C_5\text{-}C_{12})$aryl, S-$(C_5\text{-}C_{12})$aryl where aryl is optionally substituted with halo, OH or $(C_1\text{-}C_4)$ alkyl, or H;
R_5 is H, OH or absent;
R_6 is $(C_1\text{-}C_4)$ alkyl or H;
R_7 is OH or -OSi$((C_1\text{-}C_4)\text{alkyl})_3$; or
R_6 and R_7 together are ethylenedioxy;
R_8 is $(C_1\text{-}C_4)$alkyl optionally substituted with OH or halo;
the bond represented by ---- is present or absent; with the proviso that when Y is H, n is 2-4
or
a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein
Y is $-CH_2OC(O)$ $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_8)$alkyl optionally substituted with 2 OR or 1-2 halo; a monosaccharide, $-CH_2C(O)\text{-}O\text{-}(CH_2)_2\text{-}O\text{-}C(O)CH_2SH$, $-(CH_2)_2\text{-}O\text{-}(CH_2)_2W$ where W is halo; $-(C_1\text{-}C_8)$alkyl-O-$(C_1\text{-}C_8)$alkyl; $(C_6\text{-}C_{10})$ aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_4)$alkyl, $C(O)O(C_6\text{-}C_{10})$aryl wherein the aryl group is optionally substituted with 1-2 OH, halo, $(C_1\text{-}C_4)$alkyl, or $O(C_1\text{-}C_4)$alkyl; $-CH_2CO_2(C_1\text{-}C_4)$alkyl, $-CH_2CO_2H$, Si$((C_1\text{-}C_4)\text{alkyl})_3$ or an amino acid residue;
R_4 is SCH_2CO_2 $(C_1\text{-}C_4)$ alkyl, S- $(C_6\text{-}C_{10})$ aryl optionally substituted with halo, OH or $(C_1\text{-}C_4)$alkyl, or H;
R_6 is $(C_1\text{-}C_4)$ alkyl;
R_7 is OR or -OSi$((C_1\text{-}C_4)\text{alkyl})_3$; or
R_6 and R_7 together are ethylenedioxy;
or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 wherein Y is an amino acid residue; or the pharmaceutical acceptable salts thereof.

4. A compound of claims 1 having the formula



or a pharmaceutically acceptable salt thereof.

5. A compound of claim 1 or claim 2 wherein n is 1, the bond represented by ---- is present, and R_5 is absent.

6. A compound of claim 5 wherein R_3 is CH_3, R_4 is H, R_6 is CH_3, R_7 is OH and R_8 is CH_3.

7. A compound of claim 6 wherein X is O.

8. A compound of claim 7 wherein Y is CH_2OC (O) CH_3, $(C_1\text{-}C_4)$ alkyl, a $(C_1\text{-}C_8)$ alkyl substituted by 2 OH, fructose, $-(CH_2)_2Br$, $-C(CH_3)_2\text{-}O\text{-}(C_1\text{-}C_4)$alkyl, or -C(O)-O- phenyl.

9. A compound of claim 8 wherein Y is $-CH_2CH_3$; $-CH_2CH(OH)CH_2OH$, or $-C(CH_3)_2\text{-}O\text{-}CH_3$.

10. A compound of claim 6 wherein X is S.

11. A compound of claim 10 wherein Y is phenyl substituted with OH or CH_3, benzyl, $-CH_2CO_2CH_3$, $-CH_2CO_2H$, or $(C_1\text{-}C_8)$alkyl substituted by 2 OH.

12. A compound of claim 11 wherein Y is $-CH_2CH(OH)CH_2OH$.

13. A compound of claim 1 or claim 2 wherein n is 1, the bond represented by ---- is absent, X is S; Y is $CH_2CO_2CH_3$; R_3 is CH_3; R_4 is $SCH_2CO_2CH_3$; R_6 is CH_3 and R_7 is OH.

14. A compound of claim 13 wherein R_5 is H or OH.

15. A pharmaceutical unit dosage form comprising an effective tumor growth-inhibiting amount of the compound of any of claims 1 to 14 in combination with a pharmaceutically-acceptable carrier.

16. The pharmaceutical unit dosage form of claim 15 wherein the carrier is a liquid vehicle.

17. The pharmaceutical unit dosage form of claim 15 wherein the carrier is adapted for parenteral, intravenous or oral administration.

18. The pharmaceutical unit dosage form of claim 15 wherein said carrier is adapted for oral administration and said dosage form is a tablet or a capsule.

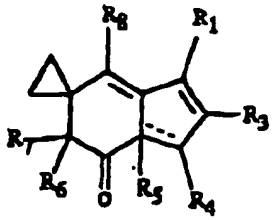
19. Use of a therapeutic amount of the compound of any of claims 1 to 14 in the manufacture of a medicament for use in a therapeutic method of inhibiting tumor cell growth in a subject in need of such therapy.

20. Use as claimed in claim 19 wherein the subject is a human cancer patient.

21. Use as claimed in claim 20 wherein the patient is afflicted with a solid tumor.

Patentansprüche

1. Verbindung der Formel

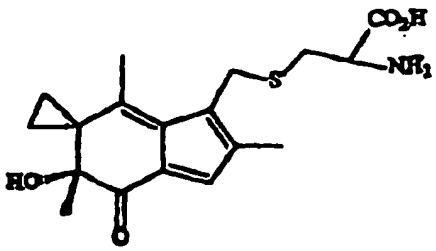


wobei R_1 $(CH_2)_n$-X-Y ist,
wobei n gleich 0 bis 4 ist;
X O oder S oder NH ist, und
Y-CH_2OC (O) (C_1-C_4) -Alkyl, (C_1-C_8)-Alkyl, wahlweise substituiert mit 2 OH oder 1-2 Halogenid; ein Monosaccharid, -CH_2C(O)-O-$(CH_2)_2$-O-C(O)CH_2SH, -$(CH_2)_2$-O-$(CH_2)_2$W, wobei W ein Halogenid ist; -(C_1-C_8)-Alkyl-O-(C_1-C_8)Alkyl; (C_6-C_{10})-Aryl, (C_6-C_{10})-Aryl(C_1-C_4)-Alkyl, C(O)O(C_6-C_{10})-Aryl, wobei die Arylgruppe wahlweise substitutioniert ist mit 1-2 OH, Halogenid, (C_1-C_4)-Alkyl, oder O(C_1-C_4)-Alkyl; -CH_2CO_2(C_1-C_4)-Alkyl, -CH_2CO_2H, Si((C_1-C_4)-Alkyl)$_3$ oder ein Aminosäurerest oder H ist;
R_3 H oder (C_1-C_4)-Alkyl ist;
R_4 SCH_2CO_2(C_1-C_4)-Alkyl, O-(C_5-C_{12})-Aryl, S-(C_5-C_{12})-Aryl, wobei Aryl wahlweise substituiert ist mit einem Halogenid, OH oder (C_1-C_4)-Alkyl, oder H ist;
R_5 H, OH oder nicht vorhanden ist;
R_6 (C_1-C_4)-Alkyl oder H ist;
R_7 OH oder -OSi ((C_1-C_4)-Alkyl)$_3$ oder
R_6 und R_7 zusammen Ethylenedioxy sind;
R_8 (C_1-C_4)-Alkyl, wahlweise substituiert mit OH oder Halogenid ist;
die durch ---- dargestellte Bindung vorhanden oder abwesend ist;
mit der Bedingung, dass wenn Y H ist, n gleich 2-4 ist, oder
ein pharmazeutisch akzeptables Salz davon.

2. Verbindung nach Anspruch 1, wobei
Y $-CH_2OC$ (O) (C_1-C_4) -Alkyl, (C_1-C_8) -Alkyl, wahlweise substituiert mit 2 OH oder 1-2 Halogenid, ein Monosaccharid, $-CH_2C(O)-O-(CH_2)_2-O-C(O)CH_2SH$, $-(CH_2)_2-O-(CH_2)_2W$, wobei W Halogenid ist; $-(C_1-C_8)$-Alkyl-O-(C_1-C_8) -Alkyl, (C_6-C_{10})-Aryl, (C_6-C_{10})-Aryl(C_1-C_4)-Alkyl, $C(O)O(C_6-C_{10})$-Aryl, wobei die Arylgruppe wahlweise substituiert ist mit 1-2 OH, Halogenid, (C_1-C_4)-Alkyl, or $O(C_1-C_4)$-Alkyl; $-CH_2CO_2(C_1-C_4)$-Alkyl, $-CH_2CO_2H$, $Si((C_1-C_4)\text{-Alkyl})_3$ oder ein Aminosäurerest ist;
R_4 $SCH_2CO_2(C_1-C_4)$-Alkyl, S-(C_6-C_{10})-Aryl wahlweise substituiert mit Halogenid, OH oder (C_1-C_4) -Alkyl, oder H ist;
R_6 (C_1-C_4)-Alkyl ist;
R_7 OH oder $-OSI((C_1-C_4)\text{-Alkyl})_3$ ist; oder
R_6 und R_7 zusammen Ethylendioxy sind;
oder ein pharmazeutisch akzeptables Salz davon.

3. Verbindung nach Anspruch 1, wobei Y ein Aminosäurerest ist; oder die pharmazeutisch akzeptablen Salze davon.

4. Vorrichtung nach Anspruch 1 mit der Formel



oder ein pharmazeutisch akzeptables Salz davon.

5. Verbindung nach einem der Ansprüche 1 oder 2, wobei n gleich 1 ist, die durch ---- dargestellte Bindung vorhanden ist, und R_5 nicht vorhanden ist.

6. Verbindung nach Anspruch 5, wobei R_3 CH_3 ist, R_4 H ist, R_6 CH_3 ist, R_7 OH ist und R_8 CH_3 ist.

7. Verbindung nach Anspruch 6, wobei X O ist.

8. Verbindung nach Anspruch 7, wobei Y $CH_2OC(O)CH_3$, (C_1-C_4)-Alkyl, ein (C_1-C_8)-Alkyl substituiert durch 2 OH, Fruktose, $-(CH_2)_2Br$, $-C(CH_3)_2-O-(C_1-C_4)$-Alkyl, oder -C(O)-O-Phenyl ist.

9. Verbindung nach Anspruch 8, wobei Y $-CH_2CH_3$; $-CH_2CH(OH)CH_2OH$, oder $-C(CH_3)_2-O-CH_3$.

10. Verbindung nach Anspruch 6, wobei X S ist.

11. Verbindung nach Anspruch 10, wobei Y Phenyl substituiert mit OH oder CH_3, Benzyl, $-CH_2CO_2CH_3$, $-CH_2CO_2H$, oder (C_1-C_8)-Alkyl substituiert durch 2 OH ist.

12. Verbindung nach Anspruch 11, wobei Y $-CH_2CH(OH)CH_2OH$ ist.

13. Verbindung nach Anspruch 1 oder 2, wobei n gleich 1. ist, die durch ---- dargestellte Bindung nicht vorhanden ist, X S ist, Y $CH_2CO_2CH_3$ ist, R_3 CH_3 ist, R_4 $SCH_2CO_2CH_3$ ist, R_6 CH_3 ist und R_7 OH ist.

14. Verbindung nach Anspruch 13, wobei R_5 H oder OH ist.

15. Pharmazeutische Einheitsdosierungsform mit einer effektiven tumorwachstumverhindernden bzw. -hemmenden Menge der Verbindung nach einem der Ansprüche 1 bis 14 in Kombination mit einem pharmazeutisch akzeptablen Träger.

16. Pharmazeutische Einheitsdosierungsform nach Anspruch 15, wobei der Träger ein flüssiger Träger ist.

17. Pharmazeutische Einheitsdosierungsform nach Anspruch 15, wobei der Träger zur parenteralen, intravenösen oder oralen Gabe eingerichtet ist.

18. Pharmazeutische Einheitsdosierungsform nach Anspruch 15, wobei der Träger zur oralen Gabe eingerichtet ist, und die Dosierungsform eine Tablette oder Kapsel ist.

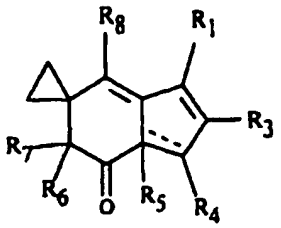
19. Verwendung einer therapeutischen Menge der Verbindung nach einem der Ansprüche 1 bis 14 bei der Herstellung eines Medikaments zur Verwendung in einem therapeutischen Verfahren zur Verhinderung bzw. Hemmung eines Tumorzellenwachstums in einem eine derartige Therapie benötigenden Subjekt.

20. Verwendung nach Anspruch 19, bei der das Subjekt ein menschlicher Krebspatient ist.

21. Verwendung nach Anspruch 20, bei der der Patient von einem festen Tumor befallen ist.

Revendications

1. Composé de formule



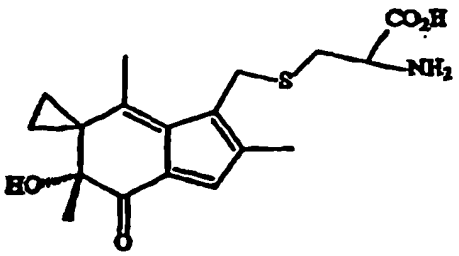
dans laquelle R_1 est $(CH_2)_n$-X-Y,
où n est de 0 à 4;
X est 0 ou S ou NH; et
Y est $-CH_2OC(O)$(alkyle en C_1-C_4), alkyle en C_1-C_8 éventuellement substitué par 2 OH ou 1-2 halogéné; un monosaccharide, $-CH_2C(O)$-O-$(CH_2)_2$-O-$C(O)CH_2SH$, $-(CH_2)_2$-O-$(CH_2)_2$W où W est halo; (alkyle en C_1-C_8)-O-(alkyle en C_1-C_8), aryle en C_6-C_{10}; (aryl en C_6-C_{10}) (alkyle en C_1-C_4), C(O)O(aryle en C_6-C_{10}) où le groupe aryle est éventuellement substitué par 1-2 OH, halo, alkyle en C_1-C_4 ou O(alkyle en C_1-C_4); $-CH_2CO_2$(alkyl en C_1-C_4), $-CH_2CO_2H$, Si (alkyle en C_1-C_4)$_3$ ou un reste amino acide ou H;
R_3 est H ou (alkyle en C_1-C_4);
R_4 est SCH_2CO_2(alkyle en C_1-C_4), O-(aryl en C_5-C_{12}), S-(aryle en C_5-C_{12}) où le groupe aryle est éventuellement substitué par halo, OH ou alkyle en C_1-C_4, ou H;
Rs est H, OH ou absent;
R_6 est alkyle en C_1-C_4 ou H;
R_7 est OH ou -OSi(alkyle en C_1-C_4)$_3$; ou
R_6 et R_7 ensemble sont un éthylènedioxy;
R_8 est un alkyle en C_1-C_4 éventuellement substitué par OH ou halo;
la liaison représentée par ----- est présente ou absente;
pourvu que quand Y est H, n est 2-4
ou
un de ses sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel
Y est $-CH_2OC(O)$(alkyle en C_1-C_4), alkyle en C_1-C_8 éventuellement substitué par 2 OH ou 1-2 halogéné; un monosaccharide, $-CH_2C(O)$-O-$(CH_2)_2$-O-$C(O)CH_2SH$, $-(CH_2)_2$-O-$(CH_2)_2$W où W est halo; (alkyle en C_1-C_8)-O-(alkyle en C_1-C_8), aryle en C_6-C_{10}; (aryl en C_6-C_{10}) (alkyle en C_1-C_4), C(O)O(aryle en C_6-C_{10}) où le groupe aryle est éventuellement substitué par 1-2 OH, halo, alkyle en C_1-C_4 ou O(alkyle en C_1-C_4); $-CH_2CO_2$(alkyle en C_1-C_4), $-CH_2CO_2H$, Si(alkyle en C_1-C_4)$_3$ ou un reste amino acide;

R_4 est SCH_2CO_2(alkye en C_1-C_4), S-(aryle en C_6-C_{10}) éventuellement substitué par halo, OH ou alkyle en C_1-C_4, ou H;
R_6 est alkyle en C_1-C_4;
R_7 est OH ou -OSi(alkyle en en C_1-C_4)$_3$; ou
R_6 et R_7 ensemble sont un éthylènedioxy;
ou un de ses sels pharmaceutiquement acceptables.

3. Composé selon la revendication 1, où Y est un reste amino acide; ou un de ses sels pharmaceutiquement acceptables.

4. Composé selon la revendication 1, de formule



ou un de ses sels pharmaceutiquement acceptables.

5. Composé selon la revendication 1 ou 2, dans lequel n est 1, la liaison représentée par ----- est présente, et R_5 est absent.

6. Composé selon la revendication 5, dans lequel R_3 est CH_3, R_4 est H, R_6 est CH_3, R_7 est OH et R_8 est CH_3.

7. Composé selon la revendication 6, dans lequel X est O.

8. Composé selon la revendication 7, dans lequel Y est $CH_2(OC(O)CH_3$, alkyle en C_1-C_4, alkyle en C_1-C_4 substitué par 2 OH, le fructose, -$(CH_2)_2$Br, -C(CH_3)2-O-(alkyle en C_1-C_4), ou -C(CO)-O-phényle.

9. Composé selon la revendication 8, dans lequel Y est -CH_2CH_3, -CH_2-CH(OH)CH_2OH où -$C(CH_3)_2$-O-CH_3.

10. Composé selon la revendication 6, dans lequel X est S.

11. Composé selon la revendication 10, dans lequel Y est un phényle substitué par OH ou CH_3, benzyle, -$CH_2CO_2CH_3$, -$CH_2CO_2H_2$, ou alkyle en C_1-C_8 substitué par 2 OH.

12. Composé selon la revendication 11, dans lequel Y est -CH_2CH(OH)CH_2OH.

13. Composé selon la revendication 1 ou 2, dans lequel n est 1, la liaison réprésentée par ----- est absente, X est S; Y est $CH_2CO_2CH_3$; R_3 est CH_3; R_4 est $SCH_2CO_2CH_3$; R_6 est CH_3 et R_7 est OH.

14. Composé selon la revendication 13, dans lequel Rs est H ou OH.

15. Forme posologique unitaire pharmaceutique comprenant une quantité efficace contre la croissance des tumeurs du composé selon l'une quelconque des revendications 1 à 14 en combinaison avec un support pharmaceutiquement acceptable.

16. Forme posologique unitaire pharmaceutique selon la revendication 15, dans laquelle le support est un véhicule liquide.

17. Forme posologique unitaire pharmaceutique selon la revendication 15, dans laquelle le support est adapté à une administration parentérale, intraveineuse ou orale.

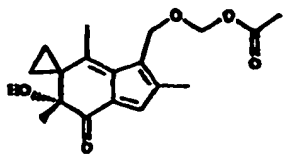
18. Forme posologique unitaire pharmaceutique selon la revendication 15, dans laquelle ledit support est adapté à l'administration orale et ladite forme posologique est un comprimé ou une capsule.

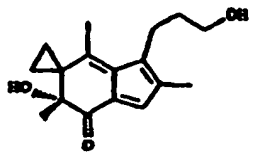
19. Utilisation d'une quantité thérapeutique du composé selon l'une quelconque des revendications 1 à 14 dans la préparation d'un médicament pour son utilisation dans une méthode thérapeutique d'inhibition de la croissance de cellules tumorales chez un sujet ayant besoin d'une telle thérapie.

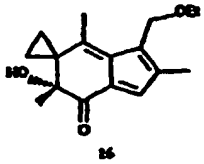
20. Utilisation selon la revendication 19, dans laquelle le sujet est un patient humain atteint de cancer.

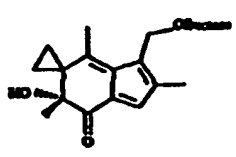
21. Utilisation selon la revendication 20, dans laquelle le patient est atteint d'un tumeur solide.

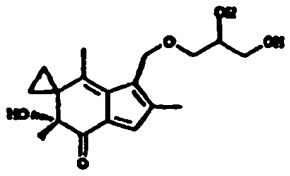
FIGURE 1

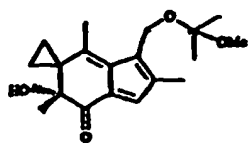


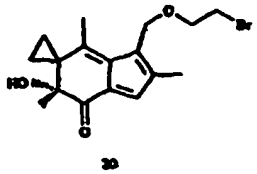












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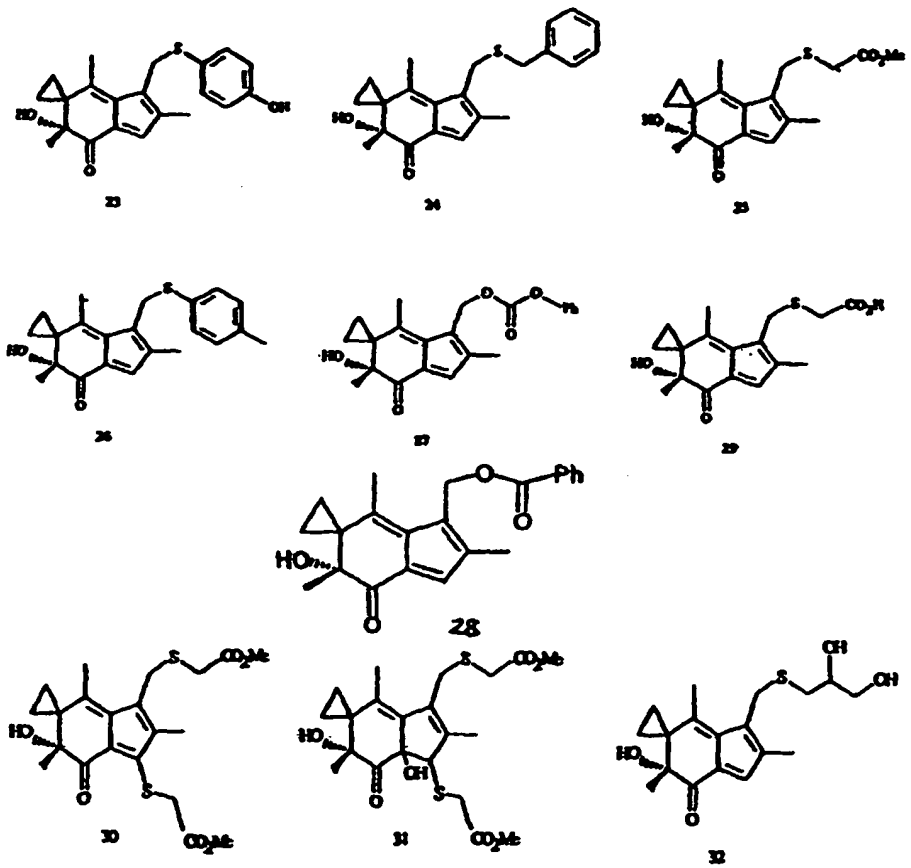

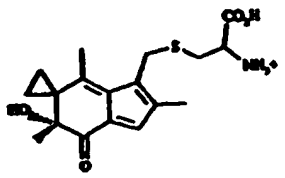

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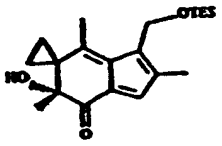

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